

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	2	6388054.pn.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 10:33			0
2	BRS	L3	1	wo-200011022-\$.did.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:14			0
3	BRS	L4	2	pya-bip-atmp	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:16			0
4	BRS	L5	36937	(tumor adj growth) or apoptosis	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:18			0
5	BRS	L6	0	4 same 5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:18			0
6	BRS	L7	2	4 and 5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:22			0
7	BRS	L8	536	stewart adj john.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:22			0
8	BRS	L9	32	chan adj daniel.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:23			0
9	BRS	L10	11	gera adj lajos.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:23			0
10	BRS	L11	2	york adj eunice.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:23			0
11	BRS	L12	14	bunn adj paul.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:24			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Error Count
12	BRS	L13	572	8 or 9 or 10 or 11 or 12	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:24			0
13	BRS	L14	2	4 and 13	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/10/23 12:24			0

=> d his

(FILE 'HOME' ENTERED AT 12:27:37 ON 23 OCT 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA'  
ENTERED AT

12:27:59 ON 23 OCT 2004

L1 0 S PYA-BIP-ATMP  
L2 0 S ACRYLOYL (P) BIPHENYLALANINE (P) PIPERIDINE  
L3 829698 S ANTITUMOR OR (TUMOR GROWTH) OR APOPTOSIS  
L4 0 S M296  
L5 18825 S STEWART J?/AU  
L6 5547 S CHAN D?/AU  
L7 448 S YORK E?/AU  
L8 1503 S BUNN P?/AU  
L9 25899 S L5 OR L6 OR L7 OR L8  
L10 447 S L9 AND L3  
L11 57942 S SMALL CELL LUNG CANCER  
L12 15223 S BRADYKININ (P) ANTAGONIST  
L13 13039 S SCLC  
L14 61690 S L11 OR L13  
L15 93 S L12 (P) L14  
L16 25 S L10 AND L15  
L17 14 DUPLICATE REMOVE L16 (11 DUPLICATES REMOVED)

=> log y

FILE 'MEDLINE' ENTERED AT 12:27:59 ON 23 OCT 2004

FILE 'CAPLUS' ENTERED AT 12:27:59 ON 23 OCT 2004

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FILE 'EMBASE' ENTERED AT 12:27:59 ON 23 OCT 2004

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FILE 'SCISEARCH' ENTERED AT 12:27:59 ON 23 OCT 2004

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FILE 'AGRICOLA' ENTERED AT 12:27:59 ON 23 OCT 2004

=> s pya-bip-atmp  
L1 0 PYA-BIP-ATMP

=> s acryloyl (p) biphenylalanine (p) piperidine  
L2 0 ACRYLOYL (P) BIPHENYLALANINE (P) PIPERIDINE

=> s antitumor or (tumor growth) or apoptosis  
L3 829698 ANTITUMOR OR (TUMOR GROWTH) OR APOPTOSIS

=> s m296  
L4 0 M296

=> s stewart j?/au  
L5 18825 STEWART J?/AU

=> s chan d?/au  
L6 5547 CHAN D?/AU

=> s york e?/au  
L7 448 YORK E?/AU

=> s bunn p?/au  
L8 1503 BUNN P?/AU

=> s 15 or 16 or 17 or 18  
L9 25899 L5 OR L6 OR L7 OR L8

=> s 19 and 13  
L10 447 L9 AND L3

=> s small cell lung cancer  
5 FILES SEARCHED...  
L11 57942 SMALL CELL LUNG CANCER

=> s bradykinin (p) antagonist  
L12 15223 BRADYKININ (P) ANTAGONIST

=> s sclc  
L13 13039 SCLC

=> s 111 or 113  
L14 61690 L11 OR L13

=> s 112 (p) 114  
L15 93 L12 (P) L14

=> s 110 and 115  
L16 25 L10 AND L15

=> duplicate remove 116  
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'  
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n  
PROCESSING COMPLETED FOR L16  
L17 14 DUPLICATE REMOVE L16 (11 DUPLICATES REMOVED)

=> d 117 1-14 ibib abs

L17 ANSWER 1 OF 14

MEDLINE on STN

DUPLICATE 1

ACCESSION NUMBER: 2002215358 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 11930011  
 TITLE: Bradykinin antagonist dimer, CU201, inhibits the growth of human lung cancer cell lines by a "biased agonist" mechanism.  
 AUTHOR: \*\*\*Chan Daniel\*\*\* ; Gera Lajos; \*\*\*Stewart John\*\*\* ; Helfrich Barbara; Verella-Garcia Marileila; Johnson Gary; Baron Anna; Yang Jie; Puck Theodore; \*\*\*Bunn Paul Jr\*\*\*  
 CORPORATE SOURCE: Lung Cancer Program, University of Colorado Cancer Center, Denver, CO 80262, USA.. Dan.Chan@UCHSC.edu  
 CONTRACT NUMBER: CA 46934 (NCI)  
 SOURCE: CA 58187 (NCI)  
 CA78154-01 (NCI)  
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2002 Apr 2) 99 (7) 4608-13. Journal code: 7505876. ISSN: 0027-8424.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200204  
 ENTRY DATE: Entered STN: 20020416  
 Last Updated on STN: 20020426  
 Entered Medline: 20020425  
 AB All small cell ( \*\*\*SCLCs\*\*\* ) and many non- \*\*\*small\*\*\* \*\*\*cell\*\*\*  
 \*\*\*lung\*\*\* \*\*\*cancers\*\*\* (NSCLCs) have neuroendocrine features including production of neuropeptides and cell surface receptors creating autocrine and paracrine growth loops. Neuropeptides bind to a family of 7-transmembrane receptors and activate heterotrimeric G proteins consisting of G(alphaq) and G(alpha12,13). Substance P derivatives (SPDs) induced \*\*\*apoptosis\*\*\* and inhibited growth of lung cancer cells by discoordinately inhibiting G(alphaq) and stimulating G(alpha12,13). However, these SPDs had low potency and short half-lives. In this report we show that a \*\*\*bradykinin\*\*\* \*\*\*antagonist\*\*\* dimer, CU201, inhibited the growth of \*\*\*SCLC\*\*\* and NSCLC cell lines with or without multidrug-resistant proteins and was 10-fold more potent with a longer plasma half-life than SPDs. \*\*\*Bradykinin\*\*\* agonists in either monomeric or dimeric form and monomeric \*\*\*bradykinin\*\*\* \*\*\*antagonist\*\*\* have no effect on lung cancer cell growth. The dimeric linking moiety of the two molecules was created, requiring a sufficient number of carbon chains to provide critical spacing between the two \*\*\*antagonists\*\*\*. CU201 inhibited intracellular Ca2+ release in response to \*\*\*bradykinin\*\*\*, indicating blockage of the G(alphaq) signal, and stimulated c-Jun kinases, indicating stimulation of the G(alpha12,13) pathway. CU201-induced \*\*\*apoptosis\*\*\* was preceded by unique changes in apparent nuclear DNA binding and by c-Jun kinase and caspase-3 activation. At the concentration at which CU201 inhibited the growth of the cancer cells, it had no effect on the growth of normal lung cells in vitro. CU201 and similar compounds offer hope of becoming a new form of targeted therapy for tumors with neuroendocrine properties.

L17 ANSWER 2 OF 14 MEDLINE on STN DUPLICATE 2  
 ACCESSION NUMBER: 2002276331 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 12006549  
 TITLE: Bradykinin antagonist dimer, CU201, inhibits the growth of human lung cancer cell lines in vitro and in vivo and produces synergistic growth inhibition in combination with other \*\*\*antitumor\*\*\* agents.  
 AUTHOR: \*\*\*Chan Daniel C\*\*\* ; Gera Lajos; \*\*\*Stewart John M\*\*\* ; Helfrich Barbara; Zhao Tom Limin; Feng Wan Yong; Chan Kenneth K; Covey Joseph M; \*\*\*Bunn Paul A Jr\*\*\*  
 CORPORATE SOURCE: Lung Cancer Program of the University of Colorado Cancer Center, University of Colorado Health Sciences Center, Denver 80262, USA.. Dan.Chan@UCHSC.edu  
 CONTRACT NUMBER: 1R43CA86581-01 (NCI)  
 SOURCE: CA 46934 (NCI)  
 CA58187 (NCI)  
 N01-CM07019 (NCI)  
 SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2002 May) 8 (5) 1280-7. Journal code: 9502500. ISSN: 1078-0432.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200210

ENTRY DATE:

Entered STN: 20020518  
Last Updated on STN: 20021018  
Entered Medline: 20021017

B

\*\*\*Small\*\*\* (\*\*\*cell\*\*\* \*\*\*lung\*\*\* \*\*\*cancers\*\*\*  
\*\*\*SCLCs\*\*\*), many non-\*\*\*SCLCs\*\*\*, and other cancers have  
neuroendocrine features, including paracrine and autocrine growth  
stimulation by various neuropeptides. Interference with this pathway is  
an attractive target for novel therapies. We developed a novel  
\*\*\*bradykinin\*\*\* \*\*\*antagonist\*\*\* dimer, CU201 (B9870), that acts as  
a "biased agonist" for neuropeptides by blocking G(alphaq) signaling and  
activating G(alpha12,13) signaling. CU201 induced \*\*\*apoptosis\*\*\* and  
complete growth inhibition in various lung cancer and other cancer cell  
lines. CU201 was 10-fold more potent than substance P derivatives and was  
stable in serum for >7 days. In this study, we evaluated the ability of  
CU201 to produce additive or synergistic growth inhibition in combination  
with various \*\*\*antitumor\*\*\* agents used in lung cancer therapy. We  
found that CU201 produced additive or synergistic growth inhibition when  
combined with doxorubicin, etoposide, cisplatin, vinorelbine, and  
paclitaxel for \*\*\*SCLC\*\*\* lines and with paclitaxel and ZD1839, an  
epidermal growth factor receptor tyrosine kinase inhibitor, for non-  
\*\*\*SCLC\*\*\* cell lines. Pharmacokinetic parameters associated with the  
i.v. administration of CU201 were evaluated in normal mice, and the  
effects of CU201 on the growth of human lung cancer xenografts were  
evaluated in athymic nude mice. In CD2F1 mice given an i.v. bolus  
infusion of 5 mg/kg, the c(max) was 5773 ng/ml (5 microM), and the decay  
was biexponential. When fitted to a two-compartment model, the  
t(1/2alpha) was 14.4 min, and the t(1/2beta) was 44.3 h, indicating a long  
terminal half-life consistent with the prolonged in vitro effects. CU201  
inhibited the growth of human lung cancers in athymic nude mice by the  
intratumoral, s.c., and i.p. routes at a dose of 5 mg/kg/day. This dose  
is >10-fold less than the dose of substance P derivatives used to inhibit  
\*\*\*SCLC\*\*\* xenografts in nude mice. We conclude that CU201 should  
undergo further preclinical toxicology studies in its development as a  
novel targeted therapy for the treatment of lung cancers with  
neuroendocrine features. These studies are in progress through the NCI  
RAID mechanism.

17 ANSWER 3 OF 14

MEDLINE on STN

DUPLICATE 3

ACCESSION NUMBER:

2002284334 MEDLINE

DOCUMENT NUMBER:

PubMed ID: 12025961

TITLE:

Bradykinin-related compounds as new drugs for cancer and  
inflammation.

AUTHOR:

\*\*\*Stewart John M\*\*\* ; Gera Lajos; \*\*\*Chan Daniel C\*\*\*  
; \*\*\*Bunn Paul A Jr\*\*\* ; \*\*\*York Eunice J\*\*\* ;  
Simkeviciene Vitalija; Helfrich Barbara

CORPORATE SOURCE:

Department of Biochemistry, University of Colorado School  
of Medicine, Denver 80262, USA.. john.stewart@uchsc.edu  
CA78154 (NCI)

CONTRACT NUMBER:

HL-26284 (NHLBI)

SOURCE:

Canadian journal of physiology and pharmacology, (2002 Apr)  
80 (4) 275-80.  
Journal code: 0372712. ISSN: 0008-4212.

PUB. COUNTRY:

Canada

DOCUMENT TYPE:

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE:

English

FILE SEGMENT:

Priority Journals

ENTRY MONTH:

200212

ENTRY DATE:

Entered STN: 20020528  
Last Updated on STN: 20021217  
Entered Medline: 20021204

AB

\*\*\*Bradykinin\*\*\* (BK) (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) is an  
important growth factor for \*\*\*small\*\*\* - \*\*\*cell\*\*\* \*\*\*lung\*\*\*  
\*\*\*cancer\*\*\* (\*\*\*SCLC\*\*\*) and prostate cancer (PC). These cancers  
have cells of neuroendocrine origin and express receptors for a variety of  
neuropeptides. BK receptors are expressed on almost all lung cancer cell  
lines and on many PC cells. Our very potent BK \*\*\*antagonist\*\*\* B9430  
(D-Arg-Arg-Pro-Hyp-Gly-Igl-Ser-D-Igl-Oic-Arg) (Hyp, trans-4-hydroxy-L-  
proline; Igl, alpha-2-indanylglycine; Oic, octahydroindole-2-carboxylic  
acid) is a candidate anti-inflammatory drug but does not inhibit growth of  
\*\*\*SCLC\*\*\* or PC. When B9430 is dimerized by N-terminal cross-linking  
with a suberimide linker, the product B9870 is a potent growth inhibitor  
for \*\*\*SCLC\*\*\* both in vitro and in vivo in athymic nude mice. Daily  
i.p. injection at 5 mg x kg(-1) day(-1) beginning on day 8 after  
\*\*\*SCLC\*\*\* SHP-77 cell implantation gave 65% inhibition of \*\*\*tumor\*\*\*  
\*\*\*growth\*\*\*. B9870 stimulates \*\*\*apoptosis\*\*\* in \*\*\*SCLC\*\*\* by  
a novel "biased agonist" action. We have also developed new small mimetic  
\*\*\*antagonists\*\*\*. BKM-570 (F5C-OC2Y-Atmp) (F5C, pentafluorocinnamic

acid; OC2Y, O-2,6-dichlorobenzyl tyrosine; Atpm, 4-amino-2,2,6,6-tetramethylpiperidine) is very potent for inhibition of SHP-77 growth in nude mice. When injected daily i.p. at 5 mg x kg(-1), M-570 gave 90% suppression of \*\*\*tumor\*\*\* \*\*\*growth\*\*\*. M-570 is more potent than the well-known anticancer drug cisPlatin (60% inhibition) or the recently developed SU5416 (40% inhibition) in this model. M-570 also showed activity against various other cancer cell lines in vitro (\*\*\*SCLC\*\*\*, non-\*\*\*SCLC\*\*\*, lung, prostate, colon, cervix) and inhibited growth of prostate cell line PC3 in nude mice. M-570 and related compounds evidently act in vivo through pathways other than BK receptors. These compounds have clinical potential for treatment of human lung and prostate cancers.

ANSWER 4 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN

SION NUMBER: 2003:509828 CAPLUS  
ENT NUMBER: 140:175313  
: Structural modifications of highly potent bradykinin antagonists and their pharmacological consequences  
R(S): \*\*\*Stewart, John M.\*\*\* ; Gera, Lajos; \*\*\*York,\*\*\*  
Eunice J.\*\*\* ; \*\*\*Chan, Daniel C.\*\*\* ; \*\*\*Bunn,\*\*\*  
Paul A., Jr.\*\*\*  
RATE SOURCE: Department of Biochemistry and Molecular Genetics,  
University of Colorado Medical School, Denver, CO,  
80262, USA  
E: Peptides 2000, Proceedings of the European Peptide  
Symposium, 26th, Montpellier, France, Sept. 10-15,  
2000 (2001), Meeting Date 2000, 945-946. Editor(s):  
Martinez, Jean; Fehrentz, Jean-Alain. Editions EDK:  
Paris, Fr.  
CODEN: 69EDWK; ISBN: 2-84254-048-4  
ENT TYPE: Conference  
AGE: English

Peptides and non-peptide \*\*\*bradykinin\*\*\* \*\*\*antagonists\*\*\* were synthesized, purified and characterized by std. methods. B-9430, which blocks both B2 and B1 receptors, is a truly outstanding \*\*\*antagonist\*\*\*. It is very potent, is totally resistant to enzymic degrdn. and is orally available. Use in this peptide of the new amino acid, .alpha.-(2-indanyl)glycine is important for conferring these remarkable properties. Higher potency was achieved with B-10206, which uses pentafluorophenylalanine and N-cycloheptylglycine. Potent and long-acting \*\*\*antagonists\*\*\* lacking the C-terminal Arg residue have been developed. Some of these are specific for B1 receptors (B-9958) or show combined B1-B2 \*\*\*antagonist\*\*\* activity (B-9858). The general desire for nonpeptide drugs has prompted the authors to develop small mol. BK \*\*\*antagonists\*\*\*. Among many compds., M-570 can be cited. While its anti-BK activity is not high, it has shown remarkable anticancer activity against small cell lung carcinoma (\*\*\*SCLC\*\*\*), both in vitro and in vivo. It is also active in vitro against prostate, colon, pancreas and breast cancer cell lines, as well as non-\*\*\*SCLC\*\*\*. The \*\*\*bradykinin\*\*\* \*\*\*antagonists\*\*\* stimulate \*\*\*apoptosis\*\*\* of cancer cells in vitro by a novel "biased agonist" mechanism; they stimulate one intracellular second-messenger pathway while inhibiting another. Taken together, these results strongly suggest that certain of these compds. should be developed as drugs for inflammation and cancers.  
ENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 5 OF 14 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

SION NUMBER: 2001:256049 BIOSIS  
IENT NUMBER: PREV200100256049  
: Bradykinin-related compounds as new drugs for lung cancer and inflammation.  
R(S): \*\*\*Stewart, John M.\*\*\* [Reprint author]; Gera, Lajos  
[Reprint author]; \*\*\*Chan, Daniel C.\*\*\* [Reprint  
author]; \*\*\*Bunn, Paul A., Jr.\*\*\* [Reprint author];  
\*\*\*York, Eunice J.\*\*\* [Reprint author]; Helfrich, Barbara  
[Reprint author]  
RATE SOURCE: Univ. of Colorado Medical School, 4200 E. Ninth Ave.,  
Denver, CO, 80262, USA  
CE: FASEB Journal, (March 7, 2001) vol. 15, No. 4, pp. A248.  
print.  
Meeting Info.: Annual Meeting of the Federation of American  
Societies for Experimental Biology on Experimental Biology  
2001. Orlando, Florida, USA. March 31-April 04, 2001.  
CODEN: FAJOEC. ISSN: 0892-6638.  
IENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 23 May 2001  
 Last Updated on STN: 19 Feb 2002

AB \*\*\*Bradykinin\*\*\* (BK: Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg) is an important growth factor for \*\*\*small\*\*\* \*\*\*cell\*\*\* \*\*\*lung\*\*\* \*\*\*cancer\*\*\* ( \*\*\*SCLC\*\*\* ). BK receptors are expressed on almost all lung cancer cell lines. Our very potent BK receptor \*\*\*antagonist\*\*\* B9430 (DArg-Arg-Pro-Hyp-Gly-Igl-Ser-DIgl-Oic-Arg) (Hyp: trans-4-hydroxy-L-proline, Igl: alpha-2-indanylglycine, Oic: octahydroindole-2-carboxylic acid) is a candidate antiinflammatory drug. When B9430 is dimerized by N-terminal crosslinking with suberimide, the product, B9870, is a potent growth inhibitor for \*\*\*SCLC\*\*\* strain SHP-77, both in vitro and in vivo in athymic nude mice. Daily i.p. injection at 5 mg/kg/day beginning on day 8 after SHP-77 cell implantation gave 70% inhibition of \*\*\*tumor\*\*\* \*\*\*growth\*\*\*. B9870 stimulates \*\*\*apoptosis\*\*\* in \*\*\*SCLC\*\*\* by a novel "biased agonist" action. We have also developed new small mimetic \*\*\*antagonists\*\*\*. M570 (F5C-OC2Y-Atmp) (F5C: pentafluorocinnamic acid, OC2Y: O-2,6-dichlorobenzyl tyrosine, Atmp: 4-amino-2,2,6,6-tetramethylpiperidine) is very potent for inhibition of SHP-77 growth in nude mice. When injected daily i.p. at 5 mg/kg, M570 gave 90% suppression of \*\*\*tumor\*\*\* \*\*\*growth\*\*\*. M570 is more potent than the well-known anti-cancer drug cisplatin (60% inhibition) or the recently developed SU5416 (40% inhibition) in this model. M570 also showed activity against various other cancer cell lines in vitro ( \*\*\*SCLC\*\*\*, non- \*\*\*SCLC\*\*\* lung, prostate, colon, cervix). M570 and related compounds evidently act through pathways other than BK receptors in vivo. These compounds have clinical potential for treatment of human lung cancers.

L17 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2000:894619 CAPLUS  
 DOCUMENT NUMBER: 134:216928  
 TITLE: Bradykinin antagonists: Anti-cancer drugs for the new millennium?  
 AUTHOR(S): \*\*\*Stewart, John M.\*\*\* ; Gera, Lajos; \*\*\*York,\*\*\*  
 Eunice J.\*\*\* ; \*\*\*Chan, Daniel C.\*\*\* ; \*\*\*Bunn,\*\*\*  
 Paul A., Jr.\*\*\* ; Helfrich, Barbara  
 CORPORATE SOURCE: Department of Biochemistry and Molecular Genetics,  
 University of Colorado Health Sciences Center, Denver,  
 CO, 80262, USA  
 SOURCE: Peptides for the New Millennium, Proceedings of the  
 American Peptide Symposium, 16th, Minneapolis, MN,  
 United States, June 26-July 1, 1999 (2000), Meeting  
 Date 1999, 219-221. Editor(s): Fields, Gregg B.; Tam,  
 James P.; Barany, George. Kluwer Academic Publishers:  
 Dordrecht, Neth.  
 CODEN: 69ATHX  
 DOCUMENT TYPE: Conference  
 LANGUAGE: English

AB The authors have shown that specialized bradykinin (BK) antagonist peptides and certain related smaller nonpeptide mols. can inhibit growth of certain lung and prostate cancers by stimulating \*\*\*apoptosis\*\*\* through a "biased agonist" mode of action. To this end the authors' investigated compds. related to the crit. C-terminal part of BK antagonist peptides and to the first reported nonpeptide BK antagonist, Dcg-2NaI-Aqu. BKM-226 was the first shortened peptide sequence dimer to show activity, and served as the "lead" compd. for further syntheses, which led to potent dimers such as BKM-516, BKM-790 and BKM-862. Among nonpeptides, potent compds. were found among both monomers (BKM-570) and dimers (BKM-620). Several of these compds. have been found to inhibit growth of tumors in vivo in athymic mice. Cancer cells were implanted s.c. in matrigel and allowed one week to establish. Mice were then injected i.p. daily with peptides at 5 mg/kg/day. The most potent compd. in vitro and in vivo found so far is BKM-638, which is active at 0.5 mg/kg/day against SHP-77. Peptide B9870 has been accepted for drug development.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
 ACCESSION NUMBER: 2000:795997 CAPLUS  
 TITLE: New class of drug candidates for lung and prostate cancer.  
 AUTHOR(S): \*\*\*Stewart, John M.\*\*\* ; Gera, Lajos; \*\*\*York,\*\*\*  
 Eunice J.\*\*\* ; \*\*\*Chan, Daniel C.\*\*\* ; \*\*\*Bunn,\*\*\*  
 Paul A., Jr.\*\*\*  
 CORPORATE SOURCE: Department of Biochemistry, University of Colorado



SOURCE: Medical School, Denver, CO, 80262, USA  
Abstracts of Papers, 220th ACS National Meeting,  
Washington, DC, United States, August 20-24, 2000  
(2000) MEDI-001  
CODEN: 69FZC3  
PUBLISHER: American Chemical Society  
DOCUMENT TYPE: Journal; Meeting Abstract  
LANGUAGE: English  
B Biased agonists, which stimulate one second messenger pathway while  
inhibiting another, can stimulate \*\*\*apoptosis\*\*\*. Agents which have  
this property combined with anti-angiogenic action offer an exciting new  
approach to anti-cancer therapy. \*\*\*Bradykinin\*\*\* (BK) is an  
autocrine growth factor for prostate and lung cancers, notably small cell  
lung carcinoma ( \*\*\*SCLC\*\*\* ). Certain BK \*\*\*antagonists\*\*\* have  
been found to cause \*\*\*apoptosis\*\*\* of \*\*\*SCLC\*\*\* and prostate  
cancer cell lines in vitro and to inhibit growth of lung cancers implanted  
s.c. in athymic nude mice. \*\*\*Tumor\*\*\* \*\*\*growth\*\*\* in vivo can  
be completely inhibited without harmful effects to the host animals. Both  
effective peptides and non-peptides have been discovered. The peptides  
used are remarkable; they are totally enzyme-resistant and are orally  
available. Potent new compds. and mechanisms of action will be presented.

17 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
ACCESSION NUMBER: 2000:288762 CAPLUS  
DOCUMENT NUMBER: 133:99226  
TITLE: Dimers of bradykinin antagonists and their smaller  
molecular mimetics as potential anticancer drugs  
AUTHOR(S): Gera, Lajos; \*\*\*Chan, Daniel C.\*\*\* ; Helfrich,  
Barbara; \*\*\*Bunn, Paul A., Jr.\*\*\* ; \*\*\*York,\*\*\*  
\*\*\* Eunice J.\*\*\* ; \*\*\*Stewart, John M.\*\*\*  
CORPORATE SOURCE: Department of Biochemistry and Molecular Genetics,  
University of Colorado Medical School, Denver, CO,  
80262, USA  
SOURCE: Peptides 1998, Proceedings of the European Peptide  
Symposium, 25th, Budapest, Aug. 30-Sept. 4, 1998 (1999  
) , Meeting Date 1998, 850-851. Editor(s): Bajusz, Sandor; Hudecz, Ferenc.  
Akademiai Kiado: Budapest, Hung.  
CODEN: 68WKAY  
DOCUMENT TYPE: Conference  
LANGUAGE: English

AB The authors have developed a series of novel \*\*\*bradykinin\*\*\* (BK)  
\*\*\*antagonist\*\*\* dimers that are potent and selective in the growth  
inhibition of human \*\*\*small\*\*\* \*\*\*cell\*\*\* \*\*\*lung\*\*\*  
\*\*\*cancer\*\*\* ( \*\*\*SCLC\*\*\* ) cells in vitro and in vivo. In addn. to  
new BK analogs with shorter chains, some BK mimetics that exhibit  
impressive growth inhibitory properties are also reported here. Peptides  
and mimetics were prepd. using both conventional soln. phase or solid  
phase methods, purified by high performance liq. chromatog. (HPLC) and  
characterized by thin layer chromatog. (TLC), laser desorption mass  
spectrometry (LDMS) and amino acid anal. The tetrazolium colorimetric MTT  
(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) growth  
assay was used to monitor the potency and cytotoxicity of BK  
\*\*\*antagonists\*\*\* and mimetics in cell lines of human lung cancer.  
B9870-2 and some BK-related mimetic analogs (BKM-294, BKM-620 and BKM-622)  
may provide a novel approach for the development of clin. useful agents  
for the treatment of human lung cancer, which is the most fatal malignancy  
in the world.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

17 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
ACCESSION NUMBER: 1999:578886 CAPLUS  
DOCUMENT NUMBER: 132:666  
TITLE: Dimers of bradykinin and substance P antagonists as  
potential anti-cancer drugs  
AUTHOR(S): \*\*\*Stewart, J. M.\*\*\* ; Gera, L.; \*\*\*Chan, D.\*\*\*  
\*\*\* C.\*\*\*  
CORPORATE SOURCE: Department of Biochemistry, University of Colorado  
Medical School, Denver, CO, 80262, USA  
SOURCE: Peptide Science: Present and Future, Proceedings of  
the International Peptide Symposium, 1st, Kyoto, Nov.  
30-Dec. 5, 1997 (1999), Meeting Date 1997, 731-732.  
Editor(s): Shimonishi, Yasutsugu. Kluwer: Dordrecht,  
Neth.  
CODEN: 68BYA5  
DOCUMENT TYPE: Conference  
LANGUAGE: English

B The authors report dimers of \*\*\*bradykinin\*\*\* (BK) and substance P (SP) \*\*\*antagonists\*\*\* and heterodimers of SP and BK \*\*\*antagonists\*\*\* that are potent selectively cytotoxic agents for \*\*\*small\*\*\* \*\*\*cell\*\*\* \*\*\*lung\*\*\* \*\*\*cancer\*\*\* ( \*\*\*SCLC\*\*\* ). Although straight-chain analogs of SP and bombesin have shown toxicity against \*\*\*SCLC\*\*\*, none of the simple BK \*\*\*antagonists\*\*\* were toxic to cells, although they were very effective for inhibition of BK-evoked elevation of intracellular free calcium in \*\*\*SCLC\*\*\* cultures. Typical of this behavior is B-9430, a very potent 'third-generation' BK \*\*\*antagonist\*\*\* which is active against both B1 and B2 BK receptors and shows a long half-life in vivo. When this \*\*\*antagonist\*\*\* was crosslinked by suberimide at the N-terminus (B-201), potent cytotoxic activity was found. Dimers of 'first-generation' BK \*\*\*antagonists\*\*\*, such as CP-127, were introduced by investigators at Cortech, and while they are quite potent \*\*\*antagonists\*\*\* in many BK assays, were not cytotoxic. When the linker in CP-127 was moved to the N-terminus of the dimer (B-197) significant toxicity was found. Even dimers of the potent 'second-generation' Hoechst \*\*\*antagonist\*\*\* HOE-140 showed only low cytotoxicity against \*\*\*SCLC\*\*\*. Orosz et al. reported that a pseudopeptide substance P \*\*\*antagonist\*\*\* (B-237) was active against \*\*\*SCLC\*\*\*. The authors confirmed this activity, and found that neither a homodimer (B-240) nor a heterodimer of this peptide with the best BK \*\*\*antagonist\*\*\* (B-215) showed increased cytotoxicity. Certain of these new dimers are toxic to \*\*\*SCLC\*\*\* lines that show multidrug resistance phenotypes, testifying to the different mechanism of toxicity of these agents. Preliminary studies indicate that these new dimers act by stimulation of \*\*\*apoptosis\*\*\* in \*\*\*SCLC\*\*\* cells. Peptide dimer B-201 inhibited the growth of \*\*\*SCLC\*\*\* cell line SHP-77 when implanted s.c. in athymic (nude) mice. These dimers offer a new avenue for anti-cancer drug development.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

17 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN

CESSION NUMBER: 1998:597936 CAPLUS

OCUMENT NUMBER: 130:567

ITLE: Potent, wide-spectrum, orally active bradykinin antagonists

UTHOR(S): \*\*\*Stewart, John M.\*\*\* ; Gera, Lajos; Whalley, Eric T.; Hanson, Wendy L.; Zuzack, John S.

ORPORATE SOURCE: Department of Biochemistry, University of Colorado School of Medicine, Denver, CO, 80262, USA

OURCE: Peptides 1996, Proceedings of the European Peptide Symposium, 24th, Edinburgh, Sept. 8-13, 1996 (1998), Meeting Date 1996, 815-816. Editor(s): Ramage, Robert; Epton, Roger. Mayflower Scientific: Kingswinford, UK. CODEN: 66RCA5

OCUMENT TYPE: Conference

ANGUAGE: English

B The authors examd. the structure-activity relationship of \*\*\*bradykinin\*\*\* \*\*\*antagonists\*\*\* contg. .alpha.-(2-indanyl)glycine (Igl). Compds. were examd. for activity on rat uterus, guinea pig ileum, rabbit aorta, B1 and B2 receptor binding, \*\*\*SCLC\*\*\* anticancer activity and anti-inflammatory activity. Acylation of the amino acid terminus of BK B2 \*\*\*antagonists\*\*\* with hydrophobic residues increases potency; acylation of B9430 with adamantaneacetic acid decreased B1 activity and gave a selective B2 \*\*\*antagonist\*\*\*. Analogs of B9430 lacking the C-terminal Arg and contg. added N-terminal basic residues are potent and persistent B1 \*\*\*antagonists\*\*\*. Monomeric compds. showed potent inhibition of calcium flux in \*\*\*SCLC\*\*\* cells, but are not cytotoxic. Some dimers, however, show potent and selectivity cytotoxicity for \*\*\*SCLC\*\*\* cultured cells; B9870 is very potent. Some of the \*\*\*bradykinin\*\*\* \*\*\*antagonists\*\*\* have potential in the treatment of chronic inflammation and in human lung cancer.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

17 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN

CESSION NUMBER: 1998:597736 CAPLUS

OCUMENT NUMBER: 130:564

ITLE: New classes of bradykinin antagonists having anti-cancer and/or anti-inflammatory activity

UTHOR(S): Gera, Lajos; \*\*\*Stewart, John M.\*\*\* ; \*\*\*Chan,\*\*\*

\*\*\* Dan\*\*\* ; Whalley, Eric T.; Zuzack, John S.; Burkard, Michael R.

CORPORATE SOURCE: Department of Biochemistry, University of Colorado  
School of Medicine, Denver, CO, 80262, USA  
SOURCE: Peptides 1996, Proceedings of the European Peptide  
Symposium, 24th, Edinburgh, Sept. 8-13, 1996 (1998),  
Meeting Date 1996, 415-416. Editor(s): Ramage,  
Robert; Epton, Roger. Mayflower Scientific:  
Kingswinford, UK.  
CODEN: 66RCA5  
DOCUMENT TYPE: Conference  
LANGUAGE: English  
3 The authors prepd. examples of third generation \*\*\*bradykinin\*\*\*  
\*\*\*antagonists\*\*\* contg. .alpha.-(2-indanyl)glycine (Igl) and examd.  
their B2 and B1 functional effects on guinea pig ileum and rat uterus (B2)  
and rabbit aorta (B1). The best full chain \*\*\*antagonists\*\*\* contg.  
Igl such as B9430 (D-Arg-Arg-Pro-Hyp-Gly-Igl-Ser-D-Igl-Ser-D--Oic-Arg) are  
extremely potent at both B1 and B2 receptors. They are orally active and  
have long persistence of action. Analogs of B9430 lacking the C-terminal  
Arg are potent and persistent B1 \*\*\*antagonists\*\*\*. The monomeric Igl  
\*\*\*antagonists\*\*\* inhibit \*\*\*bradykinin\*\*\* -evoked calcium flux in  
\*\*\*SCLC\*\*\* cells but are not cytotoxic. Some dimers of these show  
potent and selective cytotoxicity for \*\*\*SCLC\*\*\* cultured cells. Some  
of these new \*\*\*antagonists\*\*\* may have potential for development of  
drugs involving B1 and B2 receptors such as chronic inflammation or in  
situations where B1 receptors are involved. Dimeric \*\*\*antagonists\*\*\*  
may have potential in treatment of human lung cancers.  
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

17 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
ACCESSION NUMBER: 1997:572651 CAPLUS  
DOCUMENT NUMBER: 127:243292  
TITLE: Potent, long-acting bradykinin antagonists for a wide  
range of applications  
AUTHOR(S): \*\*\*Stewart, John M.\*\*\* ; Gera, Lajos; \*\*\*Chan,\*\*\*  
\*\*\*Daniel C.\*\*\* ; Whalley, Eric T.; Hanson, Wendy L.;

CORPORATE SOURCE: Department of Biochemistry and Cancer Center,  
University of Colorado School of Medicine, Denver, CO,  
80262, USA  
SOURCE: Canadian Journal of Physiology and Pharmacology  
(1997), 75(6), 719-724  
CODEN: CJPPA3; ISSN: 0008-4212  
PUBLISHER: National Research Council of Canada  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English

3 A review, with .apprx.30 refs. Actions of \*\*\*bradykinin\*\*\*  
(Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg; BK) are mediated by constitutively  
expressed B2 receptors (which require the full BK peptide chain) and by B1  
receptors (which require BK(1-8) as ligand) that are induced in  
inflammation. BK has many functions in normal and pathol. physiol.,  
including initiation of most, if not all, inflammation. BK also evidently  
functions as an autocrine stimulant for growth of \*\*\*small\*\*\*  
\*\*\*cell\*\*\* \*\*\*lung\*\*\* \*\*\*cancer\*\*\* ( \*\*\*SCLC\*\*\* ). A new  
group of BK \*\*\*antagonists\*\*\* contg. the novel amino acid  
.alpha.-(2-indanyl)glycine (Igl) provides both broad-spectrum and  
selective \*\*\*antagonists\*\*\* for all these functions. As examples,  
D-Arg-Arg-Pro-Hyp-Gly-Igl-Ser-D-Igl-Oic-Arg (B9430) is an extremely potent  
and long-acting \*\*\*antagonist\*\*\* of both B1 and B2 receptors, is  
stable against endogenous kinase enzymes, and is active in various in  
vivo models, including by intragastric administration. Acylation of B9430  
with dehydroquinuclidine-2-carboxylic acid (Dhq) gives B9562, a highly  
selective B2 \*\*\*antagonist\*\*\*. In contrast, Lys-Lys-Arg-Pro-Hyp-Gly-  
Igl-Ser-D-Igl-Oic (B9858) is a highly potent and selective B1  
\*\*\*antagonist\*\*\*. The dimer of B9430 linked at the amino terminus with  
suberimide is a potent selectively cytotoxic agent for \*\*\*SCLC\*\*\*  
cells. Results with these peptides suggest that a new generation of  
antiinflammatory and anticancer drugs may be at hand.

17 ANSWER 13 OF 14 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on  
STN  
ACCESSION NUMBER: 1997:231765 BIOSIS  
DOCUMENT NUMBER: PREV199799530968  
TITLE: A new class of peptide antagonist dimers inhibits the  
growth of human lung cancer cells in vitro and in vivo.  
AUTHOR(S): \*\*\*Chan, D.\*\*\* [Reprint author]; Gera, L.; Helfrich,  
B.; Helm, K.; Whalley, E.; \*\*\*Bunn, P.\*\*\* ;  
\*\*\*Stewart, J.\*\*\*

CORPORATE SOURCE: Dep. Med., Univ. Colo. Cancer Cent., Denver, CO 80262, USA  
SOURCE: Proceedings of the American Association for Cancer Research  
Annual Meeting, (1997) Vol. 38, No. 0, pp. 232-233.  
Meeting Info.: Eighty-eighth Annual Meeting of the American  
Association for Cancer Research. San Diego, California,  
USA. April 12-16, 1997.  
ISSN: 0197-016X.  
DOCUMENT TYPE: Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LANGUAGE: English  
ENTRY DATE: Entered STN: 2 Jun 1997  
Last updated on STN: 9 Jul 1997

7 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2004 ACS on STN  
SESSION NUMBER: 1997:331460 CAPLUS  
DOCUMENT NUMBER: 127:44206  
TITLE: Potent, long-acting, orally-active bradykinin  
antagonists for a wide range of applications  
AUTHOR(S): \*\*\*Stewart, John M.\*\*\* ; Gera, Lajos; \*\*\*Chan,\*\*\*  
\*\*\* Daniel C.\*\*\* ; whalley, Eric T.; Hanson, Wendy L.;  
Zuzack, John S.  
CORPORATE SOURCE: Department of Biochemistry, University of Colorado  
Medical School, Denver, CO, 80262, USA  
SOURCE: Immunopharmacology (1997), 36(2,3), 167-172  
CODEN: IMMUDP; ISSN: 0162-3109  
PUBLISHER: Elsevier  
DOCUMENT TYPE: Journal; General Review  
LANGUAGE: English  
A review, with 40 refs. Actions of \*\*\*bradykinin\*\*\*  
(Arg-Pro-Gly-Phe-Ser-Pro-Phe-Arg; BK) are mediated by constitutively  
expressed B2 receptors, that require the full BK peptide chain, and by B1  
receptors, induced in inflammation, that use BK(1-8) as ligand. In addn.  
to many physiol. and pathophysiol. functions, the growth factor activity  
of BK evidently allows it to act as an autocrine stimulant for  
\*\*\*small\*\*\* \*\*\*cell\*\*\* \*\*\*lung\*\*\* \*\*\*cancer\*\*\* . A new group  
of BK \*\*\*antagonists\*\*\* contg. the novel amino acid  
a-(2-indanyl)glycine provides extremely potent broad-spectrum as well as  
selective \*\*\*antagonists\*\*\* for all these functions.  
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT  
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829698 S ANTITUMOR OR (TUMOR GROWTH) OR APOPTOSIS  
0 S M296  
18825 S STEWART J?/AU  
5547 S CHAN D?/AU  
448 S YORK E?/AU  
1503 S BUNN P?/AU  
25899 S L5 OR L6 OR L7 OR L8  
447 S L9 AND L3  
57942 S SMALL CELL LUNG CANCER  
15223 S BRADYKININ (P) ANTAGONIST  
13039 S SCLC  
61690 S L11 OR L13  
93 S L12 (P) L14  
25 S L10 AND L15  
14 DUPLICATE REMOVE L16 (11 DUPLICATES REMOVED)

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